



THE
PHYSIOLOGY OF THE CARBOHYDRATES :

A REPLY TO DR PAVY'S "EPICRITICISM."

BY

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THE PHYSIOLOGY OF THE CARBOHYDRATES.

AT the conclusion of an article on our present knowledge of the Physiology of the Carbohydrates, published in the *Edinburgh Medical Journal* for December 1894, I said:—"In endeavouring to give a fair statement of the present state of our knowledge in regard to the relations of sugar in the economy I have been compelled to subject Dr Pavy's observations and theories to adverse criticism. But this I have done in no spirit of animosity, for no one can more admire the devotion with which he has given his time and energy to the investigation of a problem of such profound scientific interest and deep practical importance. The greatest compliment which one scientific worker can do another is to carefully study his work, and to frankly state his opinions upon it. For truth, like distance, is better learned by double than by single vision."

Dr Pavy has now published what he entitles an "*Epicriticism*," (J. & A. Churchill, 1895), in which, instead of taking my criticism in the spirit in which it was offered, he chooses to ascribe to me discreditable motives, and accuses me of wilfully misrepresenting his meaning for the purpose of getting the better of him in argument.

Before replying to his "*Epicriticism*," I would state, first, that my motives were simply those set forth in my article; and, secondly, that any misrepresentations of which I have been guilty were not made with malicious intent, but were the result of misconception of Dr Pavy's work.¹

¹ When I sent him the article in question I received from him the following letter:—

"35 GROSVENOR STREET,
"GROSVENOR SQUARE, W., Dec. 1, 1894.

"Dear Dr Paton,—Accept my thanks for having sent me a copy of the *Edinburgh Medical Journal* containing your communication on the 'Physiology of the Carbohydrates.'

"I recognise and appreciate the spirit in which you have written. There ought to be no personal consideration in this matter. I take it we are both actuated by the same motive, and simply seek after truth. Your statements require a rejoinder. I will deal with them *seriatim*, and furnish a categorical reply. In doing so I hope you will find that I shall keep to the maxim that I have said ought to be observed by both of us as scientists.—Yours faithfully,
"F. W. PAVY."

How far his action harmonizes with his "maxim" I can leave it to his readers to judge.

I shall take no further notice of the personal animus which Dr Pavy has unfortunately introduced into the discussion. His opinion of my character and conduct, and my opinion of his, can have no interest for anyone but ourselves, and has no bearing on the fate of sugar in the animal body.

With his dispute with the Council of the Royal Society I have nothing to do. I did not consider it "obligatory, in vindication of the position in which I stood before the Royal Society, that I should make endeavour to upset his (Dr Pavy's) work" (p. 66).¹ I was and am perfectly willing to leave the matter to be judged by physiologists familiar with the subject.

But I did object, and do object most strongly, to his publishing a book for medical men, entitled *The Physiology of the Carbohydrates*, in which not a trace of the mass of evidence opposed to his views is considered. Had he published it as a contribution to the subject addressed to physiologists already familiar with both sides of the question, such omissions might have been pardoned, but in publishing the work with such a title he is dealing in a hardly fair manner with the general medical reader.

Dr Pavy cannot expect others to have the same unbounded confidence in his work which he expresses on p. 13. However satisfactory his work may be to himself, by the rest of mankind it must be considered side by side with the work of other investigators.

A *résumé* of the work of these other investigators I attempted to give in my article, and Dr Pavy is mistaken in saying (p. 14) that I have "contented myself with drawing from the conflicting testimony existing the material that has fallen in with what I wanted." That this is not so—that I have not suppressed evidence favouring his views—he himself admits on p. 110, and he nowhere, in support of this contention, brings forward the work of others not quoted by me.

When Dr Pavy wants support for any of his statements, in spite of his contempt for the work of others, he habitually says,—“authorities” speak of this or that (pp. 103, 109, and 111), or “modern accredited authority” (p. 116) gives such and such results. Why does he not give his authorities, so that it might be possible to consider their value?

DR PAVY'S ACCUSATIONS OF MISREPRESENTATION.

Dr Pavy accuses me of consistently and persistently misrepresenting him. He says:—"It is a relief to come across a statement entirely free from misrepresentation" (p. 138), and speaks of my article as being "freely interspersed with attacks founded on unpardonable misrepresentations." As a matter of fact I find, to my sincere regret, that upon three points I have formed miscon-

¹ Throughout this article the pages refer to the reprints of my article, and to Dr Pavy's "Epicriticism."

ceptions of Dr Pavy's results which have led me to misrepresent his meaning. Let me add, however, that fortunately these points are of minor importance, and without direct bearing on the question of the fate of sugar.

The first of these is in regard to the amount of carbohydrate which Dr Pavy maintains may be cleaved off from the proteid substance, and upon this misconception certain arguments on pp. 10 and 16 of my article are founded. But if these arguments be struck out, the evidence against Dr Pavy's theory is not affected.

The second is in regard to the nature of the sugar in the blood in the general circulation. Upon it no argument is based, so that it need not be discussed here.

The third point is in regard to the range of variation in the reducing power of the alcoholic extract of the portal blood. In my statement on p. 8, the 10 should have been 18. The error is due to the printer, but I should not have allowed it to pass.

Correctly stated, in Dr Pavy's Experiment II., p. 104, *Physiology of Carbohydrates*, the first sample of blood withdrawn had its reducing power raised by sulphuric acid by 18 per cent., while the second had its reducing power raised by 27 per cent.

In Experiment II., p. 105, the first portion of blood had its reducing power raised by sulphuric acid by 20 per cent., the second portion by 30 per cent.

Taking, then, these figures instead of those given in my article, I still think that they strongly "militate against any definite conclusion being drawn from the observations."

These are the only misrepresentations with which I can charge myself. I regret that I should have allowed myself to fall into such errors, and I apologise to my readers and to Dr Pavy for having failed to truly represent his results.

Dr Pavy very bitterly complains of my misrepresentation of his consideration of Lépine's work. I do not blame myself for omitting to consider a sentence beginning (p. 111), "Weighty objections have been raised by various authorities," without any reference to the authorities, and I do not see that the use of a capital S at the beginning of my quotation injured his contention in any way.

As to the other misrepresentations with which I am charged I simply deny them, and I consider that I have represented Dr Pavy's results and arguments as fully and fairly as it was possible to do without reproducing whole pages of his book, which my readers as medical men were supposed to have read or to be about to read.

I leave it to those who will take the trouble to peruse my original article as well as Dr Pavy's "Epicriticism" to judge in how far I have dealt unfairly with him.

METHODS.

In my article the methods used by Dr Pavy were only cursorily considered. Dr Pavy defends them at considerable length, and as

the value of his work and the validity of his conclusions depend so greatly upon these methods, they require careful consideration.

1. My objection to the alcoholic method of extracting sugar on the ground that varying proportions of maltose and of the lower dextrins may be taken up will not, I think, be considered a "gratuitous innuendo" by those who know about the relative solubility of the carbohydrates in different strengths of alcohol.

Dr Pavy uses alcohol (absolute?) or methylated spirit,—a weaker spirit,—and he puts into this the water containing blood or tissue in the proportion of 30 to 400, and thus dilutes his alcohol still further. In such a spirit, even if over 90 per cent. of alcohol, the sugars and dextrins will be taken up in varying proportions. It is not as if there was a hard and fast line between carbohydrates soluble in, and carbohydrates insoluble in such alcohol, but a continuous chain of intermediate bodies exists, and the amount of these taken up or left will depend upon the amount of dilution of the alcohol. In his "Epicriticism" Dr Pavy admits this difficulty, but he does not seem to appreciate fully the modifications in his results which it may introduce.

2. In regard to Dr Pavy having shown, by "subsequent aqueous extraction" (p. 38), that all the glucose had been removed by his alcoholic extraction of blood and tissue, the results of Schenck must be borne in mind.

To the work of this observer I have already called Dr Pavy's attention, but he still continues to ignore it entirely. Coming as it does from Professor Pflüger's laboratory in Bonn, it must be received with respect, and cannot simply be ignored as Dr Pavy tries to ignore the admirable work of Panormoff, the "Privat-Dozent of the University of Kazan" (p. 128). It has a most important bearing on all Dr Pavy's work, and is worthy of his careful study and consideration.

By adding weighed quantities of pure glucose to defibrinated blood, to serum, and to each of the two proteids of the serum, Schenck found—I quote his words—"that after coagulation only a part is to be found in the filtrate. If the coagulum has been washed with water or alcohol until the watery or alcoholic extract contains no more trace of a reducing substance, and the coagulum is then boiled with dilute hydrochloric acid, reducing substances may be recovered in the fluid, which, in successful cases, correspond to the amount of sugar lost. It is highly probable from this that the glucose is combined with the albumins of the blood." In the course of his paper he indicates the difficulty introduced by the sugar naturally present. It must be remembered, too, that the deficits of sugar are not trifling, but amount to as much as 46 and 47 per cent. of the amount added, and the difficulty in the extraction of added glucose will also be experienced in extracting that normally

present. Thus the failure to get sugar on subsequent aqueous extraction does not prove that all the sugar has been removed.

3. For evidence of the presence of reducing substances other than sugar in the blood, I would refer to the researches of Otto (*Pflüg. Arch.*, Bd. xxxv. p. 467), who shows that after fermentation the blood possesses a distinct reducing power, and that the non-fermentable reducing substances vary in amount under different conditions.

4. Lastly, the cupric oxide reducing test depended on by Dr Pavy in his quantitative work is open to endless fallacy unless it is used on solutions of the carbohydrates freed from other reducing substances and other substances which, when treated with an acid, yield reducing agents. The alcoholic extract of blood and tissues contain many other substances soluble in alcohol besides sugars, and Dr Pavy takes no precaution to ascertain in how far the reduction is due to these bodies.

5. As to the extraction of glycogen, if Dr Pavy had desired his method to be accepted in the face of the results of Dietl and Vintschgau he should have given figures to show that 10 per cent. solution of caustic potash after boiling for half an hour does not destroy the glycogen. These figures he gives only now in the "Epicriticism," p. 42.

6. His method of estimating glycogen is vitiated by his alcoholic extraction of sugar. If dextrins are present they will to a large extent be left in the residue after extraction with alcohol. Dr Pavy says that these dextrins are destroyed by boiling with potash, but he does not state to what extent this destruction takes place, or what loss of carbohydrates results from it. By his method he has the possibility of the presence of varying quantities of dextrins with his "sugar" on the one hand, and with his "glycogen" on the other; and on inverting, the result expressed as glucose must give a very inaccurate and imperfect idea of the nature of the carbohydrates present.

After this further consideration, I can only say that I think the criticism of his methods in my article erred on the side of leniency, and that results obtained by the use of such methods must be misleading.

HEPATIC GLYCOGENESIS.

The great and central question at issue in Dr Pavy's work is this: Is there during life a constant production of glucose in the liver? It is upon this point that his theory must stand or fall. If the evidence here is against him, if he fails to prove that the liver is simply a sugar-stopping and not also a sugar-producing organ, his "system of knowledge" (p. 135) must collapse. In his book he ignored all evidence on the subject except that of his own work. He has now criticised some of the experiments opposed to his views, and considers them entirely valueless. I have already

indicated in my article where the reader may procure some account of the work bearing on this subject, and I would now only say that the question must be considered as a whole, and that the indirect evidence of the work of Külz, E. Voit, Demant, Böhm and Hofmann, and of Cavazzani must be kept in view, as well as the more direct observations of Bernard, Lehmann, and Seegen, and the other investigators mentioned in my article.¹

After a study of the whole question I consider that the *mass of evidence* clearly points to the *production of sugar in the liver*, and find it inconceivable that this process, which even Dr Pavy admits does occur in the liver under many different conditions during life and after death, is due to the sudden establishment of a totally new action, and not simply to the exaggeration of a normal function. That the vast majority of physiologists in all countries are of the same opinion is indicated by their teaching and writings.

I stand by all my objections to Dr Pavy's method of comparing the portal blood and blood of the right ventricle *from different animals and after death*. The animals used in his experiments on the portal blood were pithed, then the abdomen was opened, then the portal vein was exposed, then opened, and then the blood procured. I do not know how long this procedure takes, but it appears to me that whether the process is short or long, such a dead dog is in a far less normal condition than Seegen's animals. Dr Seegen might well say of Dr Pavy as he says of Seegen: "But I must speak of his work as utterly devoid of value from a physiological point of view . . . and it is a pity so much good intention and labour have been spent in so futile a way."

Another argument upon which Dr Pavy bases his objection to the glycogenic theory, namely, the condition of the urine, was not dealt with so fully in my article.

According to Dr Pavy, whenever the amount of sugar in the blood increases, a proportionate increase in the urine takes place; in fact the sugar (p. 63) "is simply filtered through the system, and escapes with the urine." (See also *Croonian Lecture*, p. 78.)

Now, Seegen finds in one case of diabetes 0.254 per cent. of sugar in the blood and 2.4 in the urine, and in another 0.314 per cent. in the blood and only 1.4 in the urine. Such results are clearly opposed to Dr Pavy's contention. Even his own figures (*Croonian Lecture*, p. 80) fail to support his conclusion. In one case he finds 0.2789 per cent. of sugar in the blood and 4.549 in the urine, and in another 0.1848 per cent. in the blood and 4.811 in the urine.

But his views on the carbohydrates of the urine afford the strongest evidence against this simple relationship between blood sugar and urine sugar.

¹ The presence of sugar in the blood in undiminished amount during starvation is a fact strongly opposed to Dr Pavy's views.

According to his observations (p. 120), after *glucose* is introduced into the circulation, there appear in the urine carbohydrates of lower reducing power even than maltose, and therefore presumably belonging to the group of polysaccharids. In fact, the sugar, according to his idea, must have undergone "the synthesizing and dehydrating" action of living protoplasm (p. 72), must have taken part in the metabolism before being excreted. How is this to be reconciled with its being simply "filtered through the system"?

I said in a foot-note in my paper published in the *Philosophical Transactions* before the appearance of Dr Pavy's *Physiology of the Carbohydrates*: "The theory of Pavy, repeated in nearly every text-book, that the liver is a sugar-destroying and not a sugar-forming organ, rests on so unsubstantial a basis, and has been so completely refuted by the work of Seegen and other investigators, that it need not be considered."¹ I am still of the same opinion, and until it is supported by better evidence than he has been able to adduce, I, for one, cannot afford the time to give it further consideration, but shall continue to look upon the liver as a sugar-producing structure. In doing so I by no means exclude the possibility of the liver also producing fats, and using its glycogen in such fat production. In fact, I hope soon to adduce evidence that the liver has this action. But to demonstrate this is not to overthrow the conception that glucose, too, is a normal product of hepatic metabolism.

CARBOHYDRATES DERIVED FROM "CLEAVAGE" OF PROTEIDS.

Among the questions of secondary importance on which we are at variance is the evidence adduced by Dr Pavy of the formation of carbohydrates by cleavage of proteids.

I am glad that my objections to any definite conclusion being drawn from the occurrence of osazone crystals without analyses should have led Dr Pavy to engage a reliable chemist to prove that these compounds are really osazones of sugar.

Dr Pavy says that what I wrote in this connexion (p. 14) supports his results. He fails to appreciate the difference between "formed from" and "cleaved off from." Perhaps an illustration will help him. I should say, for instance, that paper is "formed from" rags, but I should not say it was "cleaved off" from them. The processes in the mill, far less subtle than those in living protoplasm, cause a profound alteration very different from mere cleavage.

In considering my remarks upon the support to his theory of the formation of carbohydrates from proteids afforded by the researches of Hammersten and Kossel, Dr Pavy ignores the footnote on p. 5, in which I define what I understand by proteid,

¹ For the occurrence of inverted commas in the original footnote I have expressed my regret to Dr Pavy.

which is evidently what he too understood when his book was written. I have no doubt he failed to see the significance of the note. It is unfortunate that the word "proteid" is used in two different senses,—as an equivalent for the group of albuminous bodies, and as a term for the products of the union of these with other materials, such as hæmatin, nucleic acid, etc. It was for this reason I defined the sense in which it was used by us.

If Dr Pavy simply contends for the formation of carbohydrates from the decomposition of such bodies as nucleo-proteids and mucin, every one will agree with him. But his previous contention was that from albuminous bodies, such as egg albumin, fibrin, and the proteids of blood serum (*Physiology of the Carbohydrates*, p. 31) a carbohydrate is formed by cleavage, and this contention his "German confrère," Dr Grube, has pointed out is not supported by Kossel's work, since "the carbohydrate did not come from the albuminous base (Eiweisskern), but from the associated group (prothetische Gruppe)," p. 35.

But the question still remains: Was the albumin from which osazones were prepared by Dr Pavy free of carbohydrate bodies in mere mechanical union or loose chemical connexion, or was the carbohydrate an integral part of the molecule? Schenck's results, already considered, show that mixtures of carbohydrates with albuminous substances are formed, which may account for Dr Pavy's results. But Dr Pavy refuses to consider these observations.

As I said before, I do not deny that a carbohydrate *may be* yielded by the splitting of the proteid—the albuminous—molecule; but I did say, and still maintain, that all that Dr Pavy has yet proved is that, in the solution of proteids by caustic potash or sulphuric acid, a carbohydrate substance, convertible into sugar, is set free, which was either loosely combined with the proteid or formed an integral part of its molecule. Until the work of Schenck has been satisfactorily dealt with, an open mind must be kept on the subject. Undoubtedly the fact that an increased amount of reducing substance is obtained by the use of stronger solution of potash favours his view.

EVIDENCE OF CONVERSION OF CARBOHYDRATES TO FATS IN THE INTESTINAL EPITHELIUM.

Dr Pavy says of me (p. 4), "That without adducing a particle of evidence derived from an experimental testing of my work, he instead has sat down, and simply through the medium of his pen attacked me on every side with statements drawn from the heterogeneous mass of writings extant."

How is this statement of Dr Pavy's to be reconciled with the following (p. 131), when speaking of Dr Gulland's and my experiments, undertaken to test his theory of the action of intestinal epithelium on carbohydrates? "As regards the experiments on

feeding rats with starch and sugar, I too experimented with rats in 1858 (probably twenty years before Dr Paton commenced his medical studies) in relation to the same point," *et seq.!!*

Dr Pavy is certainly not quite just in his way of describing our experiments. He contended that carbohydrates are converted into fats in the intestinal epithelium. I do not think that I have misrepresented his theory in my previous article by failing to quote his words *in extenso*.

On January 21, 1895, Dr Gulland and I communicated a paper to the Royal Society of Edinburgh, "On the Absorption of Carbohydrates by the Intestinal Epithelium: an Experimental Inquiry into Pavy's theory of the Action of the Epithelium on Carbohydrates." This was published in the *Proceedings*, 1894-95, p. 347. This paper Dr Pavy heard me communicate to the Physiological Society in February last, and I sent a copy of it to him last July. It contains the records of various experiments made with the object of determining whether the fat observed and figured by him in the intestinal epithelium was really derived from carbohydrates.

One rabbit was fed on ordinary oats, another on oats deprived of fats by extraction with ether. One rabbit was fed on oats rich in fat, another on turnips poor in fat but rich in carbohydrates. In both cases, while the rabbit fed on fat-containing oats had fat in the epithelium, the other, though perfectly healthy and vigorous, had none.

With rats the following experiments were performed:—

One was fed on lean horse flesh, one on starch and sugar, one on ox fat. In the two former no fat was present in the cells, in the last there was an abundance.

Again, rats were fed on hard-boiled white of egg, starch, and water, and no fat was found in the epithelium, though the rats were healthy and vigorous.

We concluded from these experiments—

"1st, That the fat found in the intestinal epithelium of rabbits fed on oats is derived from the fats of the oats.

"2nd, That there is no evidence that carbohydrates are converted to fats by the intestinal epithelium in the course of absorption."

Dr Pavy does not give the title or reference to this paper! and I leave it to the reader to judge after this statement how far he is justified in saying (p. 132), "Dr Paton has since published some further matter on this subject, but it contains nothing that in reality touches my position," and in leaving his reader to imagine that my experiments were merely those of feeding rats on starch and sugar. The work of Voit and others has clearly shown that such diets are not "starvation diets," but are fully adequate to maintain the healthy life of animals.

It appears to me that Dr Pavy's theory of the action of the intestinal epithelium in stopping and assimilating carbohydrates

with the formation of fat rests on even a less substantial basis than his theory in regard to the performance of a similar function by the liver.

It seems to me that Dr Pavy makes a cardinal mistake in regard to his position when he considers himself the party attacked. It is he who is attacking. It is he who is trying to overthrow the generally accepted views of physiologists, and I regret that no abler champion should have seen fit to take up his gauntlet and to defend the position. But I think that the consensus of opinion is with me in considering *that the glycogenic theory is unshaken by his attack.*

In this reply I have endeavoured calmly and dispassionately to indicate why Dr Pavy's methods seem to me unreliable, and to show that he has adduced no satisfactory evidence that the liver merely arrests sugar and does not form it, and that the intestinal epithelium has any power of converting carbohydrates into fats; and I have pointed out the fallacies in his method of attempting to demonstrate that carbohydrates are formed by the cleavage of the molecules of egg albumin, fibrin, and such proteid substances. He may be right in his views; but what we have to consider is whether the evidence he adduces is sufficient to prove his contention.

I have not here dealt with Dr Pavy's strictures on my work on Hepatic Glycogenesis, because I desire not to confuse the issues before us. My work deals, not with the existence of hepatic glycogenesis, but with the *mode* of sugar production. I shall reply to his criticism on this at as early a date as possible, after I have been able to carry out certain further experimental investigations.

